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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/801,078	03/15/2004	Krzysztof Palczewski	029060-000200US	9475

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EXAMINER	
HUANG, GIGI GEORGIANA	
ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	10/801,078	PALCZEWSKI ET AL.	
	Examiner	Art Unit	
	GIGI HUANG	1617	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 25 February 2011 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

   a) ☒ The period for reply expires *6* months from the mailing date of the final rejection.

   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *25 February 2011*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: _____.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.

12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____

13. ☐ Other: _____.

/Fereydoun G Sajjadi/
Supervisory Patent Examiner, Art Unit 1617

Continuation of 11. does NOT place the application in condition for allowance because: Applicant's arguments filed February 25, 2011 have been fully considered but are not persuasive. The claims stand rejected and the grounds of rejection are addressed below in modified form to simply and directly address the specific arguments presented by Applicant.

Applicant's arguments filed February 25, 2011 have been fully considered but are not persuasive. The claims stand rejected and the grounds of rejection are addressed below in modified form to simply and directly address the specific arguments presented by Applicant.

Claims 52, 54, 60,62 currently stand rejected under 35 U.S.C. 103(a) as being unpatentable over Chapple et al. (Looking at protein misfolding neurodegenerative disease through retinitis pigmentosa) in view of Asato et al. (Fluorinated Rhodopsin Analogues from 10-Fluoro- and 14-Fluororetinal).

Chapple et al. (Chapple and Cheetham) teaches that retinitis pigmentosa is the most common cause of inherited blindness, and that the most frequent mutation and misfolding mutation in rhodopsin is the proline to histidine mutation at residue 23 (this is also called P23H, the protein is mutated and cannot fold properly). Chapple also addresses that the prior art supports the concept of the utility of known retinal types to be useful in improving the folding of mutant rhodopsin and as chemical/molecular chaperones to help with the stability of the folding of these mutant opsin proteins. Chapple et al. (Chapple and Cheetham) addresses that indeed there was improved folding of these mutant rhodopsin with these retinoids including 9-cis retinal.

Chapple et al. (Chapple and Cheetham) also states that they have shown that the addition of 9-cis retinal to P23H mutant opsin improved the amount of opsin that reached the plasma membrane and that another modified retinal had been shown to improve the folding of rhodopsin with the P23H mutation where Chapple states that the data suggests that retinoid can be used as chemical chaperones to stabilize the folding of mutant opsins shifting the equilibrium from aggregation towards a functional protein, particularly as vitamin A had previous shown to have some therapeutic benefit in retinitis pigmentosa. Chapple also clearly states that had the clinical outcome been on patients with the misfolding mutations in opsin/rhodopsin, that there was an expectation that the clinical outcomes might have been even better, clearly suggesting the use of the 9-cis retinoid for patients with the P23H mutation with a reasonable expectation of success (see full document, specifically Page 13). Asato et al. addressed that there are known 9-cis retinal analogs such as 9-cis 10-F-retinal and that the 9-cis-10F retinal behaved similar to the parent 9-cis-retinal wherein they are functionally equivalent; wherein it is prima facie obvious for one of ordinary skill in the art to substitute a functionally equivalent retinal such as 9-cis-10F-retinal for 9-cis retinal for its use for treating P23H retinitis pigmentosa with a reasonable expectation of success.

Response to Applicant's Arguments:

Applicant's arguments are primarily centered on the following points: the assertion that it is not obvious to use 9-cis-10F retinal; the assertion of the in vivo presence of endogenous 11-cis retinal; the assertion that Chapple et al.'s opinion for the use of chemical chaperones is derived from Saliba and Syed and that the fact of Saliba does not support the opinion statement; and the assertion for the lack of expectation of success due to aggregates in Saliba, and the assertion for impermissible "obvious to try"

Applicant's arguments are fully considered but are not persuasive and ignores the express teachings of the Chapple et al. (Chapple and Cheetham) reference by misinterpreting evidence presented by Chapple et al. and Saliba, and only looks to Saliba rather than the overall view by Chapple et al. (Chapple and Cheetham) of what is known in the art.

In regards to Applicant's assertion that the Examiner ignored evidence that the 11-cis retinal can also bind non-mutant opsin protein and only focused on the evidence of 9-cis retinal, this is not persuasive as firstly, the claims are directed to the use of the 9-cis retinal analog of 9-cis-10F-retinal, not to 11-cis retinal where Applicant's arguments are not commensurate in scope with the claims as written. Second, in regards to the assertion that one of skill in the art would look to endogenous 11-cis retinal which is in vivo rather than in vitro studies, is Applicant's unsupported opinion and is contrary to the reality of the disease; which is simply that endogenous 11-cis retinal cannot function with the mutated opsin protein as the protein does not work (is mutated). That is the reason that the patient has retinitis pigmentosa. Chapple et al. addresses that as a means to help the mutated opsin to function (i.e. folding), he looks to chaperones such as 9-cis retinal to improve folding and stability which is mutated and can yield a functional protein.

As for Applicant's assertion that the teachings of Chapple et al. are merely opinion statements; that the teachings Chapple et al. (Chapple and Cheetham) are unsupported by the Saliba reference, and the lack of expectation of success due to the Saliba reference, these assertions are inaccurate. It is noted to Applicant that their arguments for the functionality of the 9-cis retinal can be view as potential issues of enablement for their own invention. It should be noted that the formation of opsin aggresomes in human and animal models remains to be proven, and that aggresome formation could occur as a stochastic event with a frequency that is inversely proportional to the mutant protein's ability to fold correctly (as stated in Saliba). Thus, any newly formed opsin in the presence of the retinal would not result in further aggresome formation. In response to the argument, the misfolded rhodopsin (P23H) undergoes retrotranslocation and accumulation as aggresomes by saturation of the normal proteollytic machinery (Chapple). As the ADDITION of 9-cis-retinal improves the amount of opsin that reaches the plasma membrane, it is the increase in the amount of 9-cis-retinal over the background concentration that is being relied upon to affect treatment.

It is impermissible of Applicant to ignore the express teachings of the Chapple et al. reference which addresses not only what is known in the art but what the authors of Chapple et al. have discerned from not only from the work of others such as Li et al. which Chapple et al. cites as support for the use of 9-cis retinal for improving folding which also is used for P23H (see Li et al. Abstract and Page 11936 second column), but also from their own experience and work, AS THE OTHER AUTHOR OF CHAPPLE ET AL. IS DR. MIKE

CHEETHAM WHO ALSO WORKED ON THE SALIBA REFERENCE AND HIS ASSESSMENT IS BUILT ON HIS WORK INCLUDING THAT WITH SALIBA WHERE THEIR ASSESSMENT WOULD BE BASED ON WHAT IS KNOWN BY ONE OF SKILL IN THE ART AND KNOWLEDGE OF THEIR EXPERIENCE AND WORK, INCLUDING THAT OF CHEETHAM'S WITH SALIBA; CHAPPLE AND CHEETHAM (CHAPPLE ET AL.) DETERMINATION IS THE EXPRESS TEACHING THAT 9-CIS RETINAL IS USEFUL FOR ADDRESSING THE P23H MUTANT OPSIN PROTEIN IN RETINITIS PIGMENTOSA (PAGE 13 FIRST COLUMN, LAST PARAGRAPH) WHICH IMPROVED THE STABILITY OF THE PROTEIN TO BE FUNCTIONAL IN FOLDING AND STABILIZED, SUPPORTING THE USE OF RETINOIDS AS CHEMICAL CHAPERONES FOR THESE MUTANT OPSINS. Applicant's assertion is not reflective of what an author of the Saliba et al. reference is teaching and dismissing as an opinion statement. YOU CANNOT TAKE THE TEACHING OF ONE REFERENCE WHERE CHEETHAM IS A COAUTHOR AS SUPPORTIVE AND DISMISS THE TEACHING OF THE SAME COAUTHOR IN ANOTHER REFERENCE WHICH PART OF THE ART REJECTION OF RECORD, TREAT THE ART AS AN OPINION STATEMENT AS HIS ASSESSMENT IS BUILD ON THE TEACHINGS OF SALIBA ET AL WHICH HE CONTRIBUTED TO. Chapple and Cheetham (Chapple et al.) also clearly teaches and suggests that had the trial been focused on patients with the misfolding mutations, there is an expectation that it might have been even better outcomes and expressly states investigation of these methods to stabilize and promote folding the mutant opsin with these chaperones as therapies for these diseases; going to a reasonable expectation of success.

In regards to the assertion for impermissible "obvious to try", this is not persuasive and not reflective of the prima facie case established previously and restated in modified form above for convenience to address the specifics of Applicant's arguments . Chapple and Cheetham (Chapple et al.) are clear on the utility of retinals such as 9-cis retinal for the treatment of patients with retinitis pigmentosa including those with the P23H mutation with an expectation of success. Asato et al. addresses the functional equivalence of 9-cis retinal and its analog 9-cis-10F-retinal where it would be prima facie obvious for one of ordinary skill in the art to substitute the 9-cis 10F-retinal for 9-cis retinal in the treatment of retinitis pigmentosa caused by the P23H mutation with a reasonable expectation of success.

As for Applicant's argument of the cytoplasmic chaperones, Applicant is again confused in the point of Chapple and Cheetham (Chapple et al.) and the scope of the claims. The claims as written are directed to 9-cis-10F-retinal only which is chemical chaperone and the specifics and the art rejection are addressed above. Additionally, Applicant is only focused on the presence of aggresomes that Applicant does not see the point of Chapple et al. about the aggresomes. Chapple and Cheetham (Chapple et al.) are expressly addressing the utility of chaperones both cytoplasmic and chemical in terms of improving folding of the mutant protein, stabilizing the protein, transport of the protein, singularly or combinations thereof. Merely to clarify the record as the claim is not directed to cytoplasmic chaperones but only to 9-cis-10F-retinal which is a chemical chaperone; the point of the cytoplasmic chaperones is to show that the cytoplasmic chaperone (HSJ1b) which is on the outside of the (cytoplasmic face) of the endoplasmic reticulum (ER) can manipulate the folding of normal and mutant rhodopsin, as it caused the wild type to be retained in the ER (inside) and wild type and mutant rhodopsin (able to bind and fold). This is evidenced by the next sentence by Chapple and Cheetham conveniently not presented in Applicant's arguments, which states that the "data provide evidence that cytoplasmic chaperones can influence the folding and processing of rhodopsin. Understanding the specialized chaperone networks within photoreceptor will be essential to exploit the potential of cellulose chaperone machines to manipulate the folding of normal and mutant rhodopsin". In other words, the cytoplasmic chaperones were able to bind, fold (aggregate), transport through the ER (processing) with the normal (wild type) and mutant opsin protein with regards to the endoplasmic reticulum; making it a promising route to affect the folding ability of both normal (wild type) and mutated rhodopsin.

In regards to Applicant's reference to Berson, Applicant is confusing the issue. As addressed above, Chapple and Cheetham address that retinals such 9-cis retinal can be useful in the treatment of retinitis pigmentosa such as its most common form, P23H. Chapple and Cheetham (Chapple et al.) address that retinals such as vitamin A are known to have some therapeutic value in retinitis pigmentosa (RP) which is in line with the utility of the retinals like 9-cis retinal presented by Chapple and Cheetham (Chapple et al.) for the treatment of retinitis pigmentosa forms like P23H. Applicant asserts that there is insufficient suggestion to try as Berson's data does not provide an expectation of a successful result, but takes the Berson citation in Chapple et al. out of context and ignores the express teaching of Chapple and Cheetham. As addressed above, the reference to the vitamin A is to show that it has some therapeutic value in RP and is consistent with the express teaching of Chapple and Cheetham (Chapple et al.) for the use of 9-cis retinal for the treatment of retinitis pigmentosa P23H. Chapple and Cheetham (Chapple et al.) also clearly teaches and suggests that had the trial been focused on patients with the misfolding mutations, there is an expectation that it might have been even better outcomes and expressly suggests investigation of these methods to stabilize and promote folding the mutant opsin with these chaperones as therapies for these diseases; going to a reasonable expectation of success. As addressed above, it is impermissible of Applicant to ignore the express teachings of the Chapple et al. (Chapple and Cheetham) reference which addresses not only what is known in the art but what the authors of Chapple et al. have discerned from not only from the work of others such as Li et al. which Chapple et al. cites as support for the use of 9-cis retinal for improving folding which also is used for P23H (see Li et al. Abstract and Page 11936 second column), but also from their own experience and work where the reference teaches the utility of the 9-cis retinal for P23H retinitis pigmentosa and its utility in patients with the condition with a expectation of success.

As for Applicant's assertion that 9-cis retinal and 9-cis-10F retinal are not functionally equivalent as the relevant functionality is to binding to P23H mutant opsin, this is not persuasive as Asato clearly addresses that the fluorine substitution on the 10 position of 9-cis retinal yields a retinal with behavior similar to the parent and produced normal pigments that had similar rhodopsin profiles which Asato clearly states is not unexpected, establishing a functional equivalence of the 9-cis retinal and its fluorine substituted analog 9-cis-10F retinal, not only is it prima facie obvious to substitute the functionally equivalent 9-cis-10F for 9-cis retinal, there is a reasonable expectation of success for its protein activity (pigment formation) whether with normal protein or a mutant protein as they are functional equivalents absent data evidence of criticality.

Claim 55 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Chapple et al. (Looking at protein misfolding neurodegenerative disease through retinitis pigmentosa) in view of Asato et al. (Fluorinated Rhodopsin Analogues from 10-Fluoro- and 14-Fluororetinal) as applied above, in view of Grant et al. (Treatable forms of Retinitis Pigmentosa Associated with Systemic Neurological Disorders-Abstract). Applicant's arguments are directed to Chapple et al. (Chapple and Cheetham) in view of Asato which are addressed

above.

Claims 56-59, 61 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Chapple et al. (Looking at protein misfolding neurodegenerative disease through retinitis pigmentosa) in view of Asato et al. (Fluorinated Rhodopsin Analogues from 10-Fluoro- and 14-Fluororetinal) as applied above, in view of Lang (Ocular drug delivery conventional ocular formulations) and Geroski et al. (Drug Delivery for Posterior Segment Eye Disease). Applicant's arguments are directed to Chapple et al. (Chapple and Cheetham) in view of Asato which are addressed above.